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ABSTRACTS

Intensive Care Unit Patients

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THE RATIONALE FOR HIGHER DOSE LEVOFLOXACIN IN THE SERIOUSLY COMPROMISED HOST

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BACKGROUND/OBJECTIVE: Advances in cancer chemotherapy and supportive care continue to be associated with improved survival rates and better patient quality of life. One unwelcome consequence of these developments, however, is an increased vulnerability to serious, often life-threatening infection. Many of them are due to traditional pathogens that have acquired resistance to multiple antimicrobial agents; others are caused by commensals and relatively avirulent organisms. Current antibacterial offerings are under stress and there are few new agents on the horizon. One bedrock strategy for dealing with this threat remains combination therapy; another approach, one that has received insufficient attention, is to maximize the utility of each of our antibacterial drugs by dosing them more rationally. The purpose of this paper is to summarize the rationale for utilizing higher doses of levofloxacin in the management of immunocompromised hosts with serious infections.
METHODS: We have reviewed and will report on all available microbiologic, pharmacokinetic, pharmacodynamic, clinical efficacy, and safety data from subjects and patients exposed to daily levofloxacin doses of 750 mgms or more.
RESULTS: Even after more than seven years of extensive use in the US, levofloxacin has maintained its excellent susceptibility profile. Drug levels seen in infected patients are significantly higher than those achieved in healthy volunteers and enable coverage of organisms with higher MICs. Because of its concentration-dependent bactericidal activity, higher doses of levofloxacin increase the speed and thoroughness of bacterial eradication in vitro and can inhibit the emergence of fluoroquinolone resistance in studied organisms. Clinical trials of the 750 mgms dose form have been undertaken in complicated skin and skin structure infections, nosocomial pneumonia, and febrile neutropenia; results were at least comparable to standard, intensively administered comparator agents. Use of the same dose in community-acquired pneumonia has allowed for more rapid resolution of symptoms and a shortening of the course from ten to five days. Dosing in healthy volunteers has been taken as high as 1500 mgms per day, without significant alteration of the adverse events profile. Clinical trial data show that the safety and tolerability of 750 mgms daily are similar to those of the 250 and 500 mgms forms.
CONCLUSION: Levofloxacin has amply documented efficacy and safety credentials at clinical doses of at least 750 mgms once daily. Its higher target tissue levels and broader microbiologic reach at that drug exposure make it an attractive candidate for monotherapy of some infections in the immunocompromised host or for combination therapy with such other agents as the carbapenems or 4th generation cephalosporins. Additional clinical trials using these approaches seem warranted by the experience to date.

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TRANSCRIPTIONAL ANALYSIS OF PURIFIED CIRCULATING T CELLS FROM TRAUMA PATIENTS REVEALS UNIQUE GENE INTERACTIONS UNDETECTED IN ANALYSIS OF WHOLE LEUKOCYTES

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Variation in the composition of trauma patients' circulating leukocyte subpopulation over time post injury (PMN increased, T cells decreased) may affect detection of cell specific gene expression. Consequently, unique post-traumatic gene expression might be revealed if microarray analysis were performed on purified T cells or MO, as well as on total circulating blood leukocytes.

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METHODS: Trauma-activated genes from 5 trauma Pts with multiple organ failure and 5 matched controls (Con) were compared using Affymetrix microarray analysis (U133A GeneChip®) in various cell populations: (1) total leukocytes (erythrocyte lysed = LYSIS prep); (2) enriched MO or T cells (commercial RosetteSep™); (3) further purified MO or T cells (Miltenyi column). The microarray analysis included software, which displayed gene expression changes as altered gene interactions. Flow cytometry was performed to phenotype each cell population using T cell markers (CD2, CD3), MO markers (CD14, CD33), and markers for NK (CD56), PMN (CD66b), and B cells (CD19). Mean and St Dev were compared for Pts and controls.
RESULTS: The LYSIS prep had increased PMN (80% Pts vs. 58% Con) but fewer T cells (7% vs. 29%). 432 (49↑, 383↓) genes were detected as uniquely altered in Pt LYSIS prep. An additional 678 (60↑, 618↓) altered genes were uniquely detected in isolated Pt MO and 1573 (1082↑, 491↓) in their isolated T cells. Some gene alterations in the Pt LYSIS reflected not altered T cell gene expression, but T cell depletion, as these same genes were unchanged in parallel isolated Pt T cells. Expression of several novel apoptotic and regulatory genes was increased in isolated Pt T cells but decreased or unchanged in MO and LYSIS.
CONCLUSIONS: Transcriptional analysis of Pt circulating whole leukocyte population detected trauma-activated genes, but additional biologically relevant gene expression was revealed in leukocyte subpopulations. Possibly novel apoptotic and regulatory T cell gene interactions were also revealed.
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STUDY OF MICROBIAL BIOFILM WITH SPECIAL REFERENCE TO CANDIDA INFECTION

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Advances in medical and surgical therapies over the last two decades have led to an increasing number of immunocompromised individuals who need extensive care in specialised units like Intensive Care Units and are exposed to an increasing number of bacterial and fungal infections, many of which are centered on implanted devices used in them.
OBJECTIVES: To study the spectrum of microbial flora of the luminal biofilm associated with endotracheal tubes/intravenous cathetors in ICU patients with special reference to Candida. -To study the pathogenecity of Candida spp. -To attempt to characterise and type the *Candida albicans* strains.
METHODS: 91 indwelling device samples were collected from 75 general medical/postop patients admitted to ICU of Lok Nayak hospital for more than 48 hours and processed for microscopy (light and electron) and qualitative and quantitative cultures. Duplicate blood samples and other relevant samples were also collected and processed. Bacterial and fungal isolates ewre identified. Candida isolates were tested for virulence properties by adherence assay and were also typed by morphotyping and resistotyping.
RESULTS & CONCLUSIONS: The patients belonged to a wide age group of 0—75 years with male:female ratio of 1.8:1.The most common risk factors for ICU infections was presence of indwelling device (100%) followed by duration of stay of more than 1 week (96%) and smoking (32%). Medical condition was the most frequent underlying condition followed by trauma and surgical condition. Biofilm was demonstrated in 80 indwelling devices. Bloodstream infection was seen in 18 cases (24%) followed by UTI in 15 cases (20%). *E. Coli* was the commonest bacterial isolate while *Candida albicans* and *Candida tropicalis* were the commonest fungal isolates. Virulence markers in Candida spp. were seen to correlate well with their pathogenic potential and the typing procedures used in combination were found to be highly useful.

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CARBAPENEM RESISTANCE MECHANISMS IN ICU ISOLATES FROM TWO KUWAITI HOSPITALS

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OBJECTIVE: To characterize the mechanisms responsible for reduced susceptibility to carbapenems in bacterial isolates from intensive care unit (ICU) patients admitted to the Amiri and Farwaniya Hospitals, Kuwait.
METHODS: Bacterial isolates from ICU patients were identified using the Vitek and API 20E and NE system. Reduced carbapenem susceptibility was detected using the Vitek system and/or Kirby-Bauer method. Organisms were screened for metallo and serine beta-lactamases using inhibitors including EDTA, mercaptopropionic acid and clavulanate. Permeability studies were conducted using outer membrane permeabilizers including trisodium citrate and sodium polyphosphate. Isoelectric focusing studies were carried out in polyacrylamide gels and the enzymes detected with nitrocefin.
RESULTS: Strains showing carbapenem minimum inhibitory concentrations (MIC) of $\geq$4 mg/L were further investigated. These included *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and

Stenotrophomonas maltophilia isolates. Metallo -enzymes were found in *P. aeruginosa* and *S. maltophilia*. The *P. aeruginosa* enzyme was similar to IMP-1 and the *S. maltophilia* enzyme to L-1. A.baumannii isolates contain a serine enzyme similar to OXA-25 and 26. Reduced permeability to carbapenems was found in *Paeruginosa* and *A. baumannii*. We have not found carbapenem resistance in *Enterobacteriaceae*.
CONCLUSIONS: Carbapenem resistance has been found in isolates from ICU patients in Kuwait. Several resistance mechanisms have been detected. Metallo-beta-lactamases are responsible for high level resistance (MIC $\geq$ 16 mg/L). Serine beta-lactamases or reduced permeability, are responsible for low level resistance (MIC 4—8 mg/L).

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PHYSIOLOGICAL IMPACT OF CICLOSPORIN A AND A NON-IMMUNOSUPPRESSIVE ANALOGUE OF CICLOSPORIN A IN A MURINE MODEL OF SEPSIS: DIRECT MITOCHONDRIAL PROTECTION RATHER THAN ANTI-APOPTOTIC EFFECT?

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OBJECTIVE: To study the effects of ciclosporin A (CsA) and NIM 811, a non-immunosuppressive analogue of CsA, on pro-apoptotic pathways in a murine model of severe sepsis by caecal ligation and puncture (CLP).
METHODS: C57BL6 mices were submitted to CLP with a 21-G needle. 48 h-survival studies, detection of oligonucleosomes (at 6 h, 14 h, and 36 h post-CLP) and assessment of caspases 3 and 9 activation (at 14 h) were performed in the following groups: sham-operated, CLP, CLP + CsA, and CLP + NIM 811. CsA or NIM 811 was administered subcutaneously immediately after the surgical procedure.
RESULTS: Compared with CLP, CsA (2 and 10 mg/kg) improved 48 h-survival in CLP mices (respectively 32% vs. 100% and 60%; $p < 0.05$). NIM 811 (2 mg/kg) dramatically improved survival in CLP mice (100% vs. 32%; $p < 0.05$). Compared with sham, heart nuclear apoptosis assessed by detection of oligonucleosomes was increased at 14 h post-CLP ($p < 0.05$), which was prevented in CsA (2 mg/kg) but not in NIM 811 treated CLP mices. No significant difference was observed between sham, CLP, and CsA groups for caspases 3 and 9 activation levels at 14 h-post CLP.
CONCLUSIONS: Significant improvement of 48 h-survival was obtained with CsA and NIM 811 in a clinically relevant model of severe sepsis. The beneficial impact of NIM 811 on survival excludes a calcineurin-dependent mechanism in this model. Low heart nuclear apoptosis in this CLP model is transient, and its low intensity is likely insufficient to explain improved survival rate with inhibitors of mitochondrial permeability transition pore.

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RESPIRATORY VIRUS INFECTIONS IN INTENSIVE CARE UNIT PATIENTS IN SÃO PAULO, BRAZIL

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OBJECTIVES: Evaluate the prevalence of respiratory virus (RV) infections (RSV, adenovirus, influenza virus and parainfluenza) in patients admitted to the ICU of the Department of Internal Medicine, evaluate the impact of RV infections in the morbidity and mortality of these patients, and evaluate the ratio of these infections that are of nosocomial origin.
METHODS: Nasopharyngeal washes (NW) were taken twice a week from 174 adult patients admitted to the University Hospital ICU from May 2003 to March 2004. Samples were analyzed by direct immunofluorescence assay (DFA) (Imagen®, DAKO, UK).
RESULTS: 410 samples were taken from 174 patients irrespective of the presence of respiratory symptoms. The median age of the study population was 55 (16—92) years and 50.6% of the patients were male. Seven patients (0.04%) tested positive by DFA during the study period (6 influenza A and 1 parainfluenza infection). The interval between hospital and ICU admission and the length of the ICU stay were greater among patients with positive results (13.71×7.26 days and 14×10, 34 days, respectively). Three patients (3/7) had positive results 15, 25 and 29 days after of hospital admission and the remaining four tested positive up to 4 days after hospital admission (1, 1, 2 and 4 days). Patients with diabetes mellitus were more likely to acquire RV infection as compared to non-diabetes patients (71.4%, $p = 0.02$). The presence of other co-morbid diseases (cardiac disease, arterial hypertension, cerebral vascular disease, COPD/asthma, cancer, renal failure, bone marrow transplant, solid organ transplant, rheumatologic diseases and AIDS) or the APACHE, use of mechanical ventilation, evolution to septic shock or dead were similar between RV infected and non-infected patients.
CONCLUSIONS: The prevalence of respiratory viruses infection in ICU patients was 0.04% in this series. Three of the seven RV infections (42.8%) were considered of nosocomial origin.

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MONITORING OF CANDIDA SPP. IN SURGICAL ICU IN CANCER HOSPITAL FOR 115 MONTHS

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OBJECTIVE: To study pattern and isolation rate of Candida spp. in surgical ICU.
METHODS: Candida spp. isolated from various pathologic materials from cancer patients admitted in IX—2002—XI—2003 in ICU after extensive and combined operations for esophageal cancer, gastric cancer, colorectal cancer etc. were analyzed. Selective medium ''Chromagar'' (Bio-Rad) and automatic analyzer ''ATB-Expression'' (Bio-Merrieuz. France) were used for identification.
RESULTS: 626 bacterial and fungal strains for 817 pathologic materials were isolated, including 121 strains of Candida spp. (19.3%), *C. albicans* was the predominant strain that was isolated in 58 of 121 cases (47.9%). Two strains of Candida non-albicans were isolated from blood in patients in septic patients in whom the same species was isolated from more than one other loci. Wounds were infected with mixed micro flora including Candida spp. in patients who have previously received 2 or 3 lines of antimicrobial therapy and all patients had Candida non-albicans from wound discharge/drains. Twenty eight *C. albicans* and 16 Candida non-albicans were isolated from sputum and 26 *C. albicans* and 27 C. non-albicans were isolated from bronchoscopic materials (brushes) in patients with clinical and radiographic evidence of pneumonia. Prevalence of *C. albicans* in sputum may be explained as this material was taken from less severely ill patients, than bronchoscopy, which was undertaken in critically ill patients. Urine was colonized for 4 *C. albicans*, and 13 Candida non-albicans. All patients had urinary catheters and did not have clinical evidences of urinary infection. Non-albicans Candida consisted of *C. glabrata*—30 (24.8%), *C. parapsilosis*—13 (10.8%), *C. krusei*—6 (5%), *C. inconspicua/norbegensis*—5 (4.1%), *C. tropicalis*—3 (2.5%), *C. kefyr*—2 (1.7%), *C. Globosa*, *C. sake*, *C. lusitaniae*, *C. dubliniensis*—1 strain each (0.8%).
CONCLUSION: ICU patients often suffer from severe infectious complications and are treated with broad spectrum antibiotics, resulting in fungal colonization and super infections. The cause Candida non-albicans colonization and infections may be extensive and inappropriate prophylactic use of fluconazole.

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FUNGAL INFECTIONS IN ICU PATIENTS

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OBJECTIVE: to document fungal infection in patients admitted to the ICU in the University Teaching Hospital (UTH).
METHODS: This was a retrospective study of ICU patient records from January 1—December 2002. The study population was 518. Data analysis was done using Epi info version 6. The Fishers test-2 tail probability was used to determine associations between factors when expected frequency was less than 5. Otherwise the Chi-squared test was used to determine association between factors. A result yielding a p value of more than five percent was considered statistically insignificant.
RESULTS: The median age (Q1, Q3) of the patients was 31 (22,46) years and 56% of them were males. Fungal infections, namely cryptococcal meningitis was found in 2 (0.39%) patients. Other infections included bacterial meningitis 10 (1.93%), HIV 2 (0.39%), pneumonia 7 (1.35%), tuberculosis 8 (1.54%), tetanus 14 (2.70%), Guillain-Barre Syndrome (GBS) 3 (0.58%), septicemia 8 (1.54%) and HIV/GBS 1(0.19%). There was no association between invasive procedure and outcome ($p = 0.53$) at 95% confidence level. There was 18% risk of acquiring infection from invasive procedure ($RR = 1.18$, $0.78 < RR < 1.79$).
CONCLUSION: Fungal infection in ICU patients was cryptococcal meningitis. There is minimal risk of acquiring infection from invasive procedure. Therefore blood cultures must be mandatory in all patients admitted to ICU to reduce this risk.